I. EXECUTIVE SUMMARY

Paecilomyces lilacinus is a naturally occurring fungus commonly found in soils. It produces distinctive lilac-colored colonies. Unlike many other *Paecilomyces lilacinus* strains, *P. lilacinus* strain 251 does not produce mycotoxins or paecilotoxins, as shown by chromatographic analyses and lack of toxicity to mammals and other organisms. In laboratory studies, it grows optimally at 21-27 degrees C, and does not grow or survive above 36 degrees C. *This strain was isolated from infected nematode eggs in the Philippines, and correctly described taxonomically in 1974. As a pesticide active ingredient, P. lilacinus* strain 251 *will be used to control plant root nematodes on many food and non-food crops. It acts by infecting eggs, juveniles, and adult females of various plant pathogenic nematodes including Meloidogyne* spp. (root knot nematodes); *Radopholus similis* (burrowing nematode); *Heterodera* spp. and *Globodera* spp. (cyst nematodes); *Pratylenchus* spp. (root lesion nematodes).

Toxicology, Human Exposure, and Risks

Evaluations of mammalian toxicology data comply with the Food Quality Protection Act (FQPA) of 1996, and are sufficient to support the conditional registration of this microbe as a nematicide. Based on the absence of toxic effects at the maximum doses tested, the active ingredient is categorized as Toxicity Category III for acute oral and acute dermal toxicity. It is classified as Toxicity Category IV for acute dermal irritation and acute eye irritation. No adverse effects were seen in a toxicity/pathogenicity pulmonary study, and a comparable intraperitoneal study is categorized as supplemental. The active ingredient is not a dermal sensitizer. A waiver was granted for an immune study. [Section III.B.1]

Food Tolerances

This is the first proposed U.S. registration for *Paecilomyces lilacinus* strain 251. For this Section 3(c)(7)(C) conditional registration, a permanent exemption from the requirement of a tolerance *on all food commodities is being established.*

FQPA Considerations

The Agency has considered Paecilomyces lilacinus strain 251 *in light of the safety factors of the Food Quality Protection Act (FQPA) of 1996, and has made a determination of reasonable certainty of no harm to the U.S. population in general, and to infants and children in particular. The fungus is normally found in the environment, and its use as a pesticide active ingredient is not expected to increase exposure above background levels.*

In this assessment, no acute, subchronic, chronic, immune, endocrine, or nondietary exposure issues have been identified that may have any incremental adverse effects on infants, children, or the general U.S. population. Based on the toxicology studies, a safety factor is not required for residues of *Paecilomyces lilacinus* strain 251.

Dietary exposure and risk are not likely to increase as a result of use of *Paecilomyces lilacinus* strain 251 *in pesticide products.* Potential risks via exposure to drinking water or runoff will be minimal because the fungus moves through soil slowly and attaches to plant root nematodes. Inhalation exposure is unlikely because the product is applied directly to soil as a liquid preparation. *Furthermore, there is no indication that the fungus shares any common mechanisms of toxicity with other active ingredients to affect cumulative exposure and risk to this pesticide [Section III.B.8]. Thus, the proposed uses of P. lilacinus* strain 251 *as a pesticide are not likely to cause any incremental risk to infants, children, or adults.*

Occupational and Residential Exposure and Risk

Potential exposure of workers and pesticide handlers to Paecilomyces lilacinus strain 251 *is not expected to pose any undue risk. Worker exposure and risk are minimized by the requirement that workers use appropriate Personal Protective Equipment (PPE) and by a Restricted-Entry Interval (REI) of 4 hours.* Residential exposure and risk are not expected because the active ingredient is not toxic or pathogenic to mammals, and is not approved for residential use. *[Section III.B.4].*

Ecological and Environmental Exposure and Risks

No adverse effects are expected at field concentrations of the active ingredient, based on studies on non-target organisms including insects, beneficial nematodes, rainbow trout, *Daphnia magna*, predatory mites, and single cell green algae.

Waivers were granted for toxicity studies on birds, honeybees, wild mammals, and estuarine vertebrates and invertebrates, for the following reasons. Bird and honeybee exposures will be very low; the microbe does not grow at bird or mammalian body temperatures; several hymenopteran species were not harmed when tested with *Paecilomyces lilacinus* strain 251; no adverse effects were seen in laboratory mammalian studies; data from freshwater organisms are sufficient to cover estuarine organisms.

Based on the expected field concentrations and the general lack of toxicity seen in non-target organisms, no increased risks are expected from pesticidal use of *Paecilomyces lilacinus* strain 251 according to label directions.

D. Data Requirements

The Biopesticides and Pollution Prevention Division (BPPD) has reviewed these submissions to ensure they comply with Agency data requirements for granting this conditional registration under Section 3(c)(7)(C) of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA). For *Paecilomyces lilacinus* strain 251*, the product identity and analysis data, as well as the information submitted for acute mammalian toxicology and ecological effects are sufficient to allow the proposed use patterns. Based on evaluations of the submitted data and information, as discussed in this document, the Agency foresees no unreasonable adverse effects to human health or the environment from the use of* *Paecilomyces lilacinus* strain 251 as labeled. Under the terms of the conditional registration, granted on March 30, 2005, the registrant is required to submit the following information.

The registrant must submit an acceptable Intraperitoneal Toxicity/Pathogenicity Study, (OPPTS guideline # 885.3200) to complete the pathogenicity requirements for an unconditional registration. In the submitted intraperitoneal injection study, MRID # 460042-01, uncertainty in the test dose caused the study to be considered supplemental rather than acceptable. The Agency generally requires two pathogenicity studies to grant a full registration to a live microbial active ingredient. The registrant has submitted one acceptable pathogenicity study; therefore, a second one is needed.

II. OVERVIEW

A. Product Overview

- **Microbial Pesticide Name:** *Paecilomyces lilacinus* strain 251
- **Depository Number**: AGAL 89/030550. (Australia)
- **Trade Name(s):** MeloCon WG; Paecil; BioACT WG; Nemachek
- **OPP Chemical Code**: PC Code 028826
- **Basic Manufacturer:** Prophyta Biologischer Pflanzenschutz GmbH (Germany)
- **US Agent:** WF Stoneman Co. LLC, PO Box 465, McFarland, WI 53558-0465

B. Use Profile

Type of Pesticide: Microbial nematicide

Mechanism of action: *P. lilacinus* strain 251 parasitizes and subsequently kills eggs, juveniles, and adult females of various plant parasitic nematodes.

Use Sites:

Terrestrial Food: Vegetables, bananas, pineapples, grapevines, strawberries, and citrus, peach, and nut trees.

Terrestrial Non-Food: Ornamentals, tobacco, turf

Target Pests for Active Ingredient: Plant parasitic nematodes in soil. Examples include *Meloidogyne* spp. (Root knot nematodes); *Radopholus similis* (Burrowing nematode); *Heterodera* spp. and *Globodera* spp. (Cyst nematodes); *Pratylenchus* spp. (Root lesion nematodes); *Rotylenchulus reniformis* (Reniform Nematode); *Nacobbus* spp. (False Root-knot Nematodes).

Formulation Type: End product is formulated as a water dispersible granule containing 6.0% by weight of active ingredient.

Method and Rates of Application:

Timing: Varies with crop. In general, 14 days pre-plant; just before planting, 6 weeks after planting, repeat every 6 weeks to 4 months
Rates of Application: Maximum application: 0.24 pounds ai per acre; 4 pounds of product per acre.

Method of Application: Apply fungal suspension to agricultural soil through drip irrigation, or water in the suspension around base of each plant. If neither of these methods is possible, spray the soil surface around the base of each plant, and drench in afterwards using the irrigation system.

C. Estimated Usage

Because this is a new active ingredient, it is not possible to estimate usage.

D. Data Requirements

Submitted data satisfy the requirements for a conditional registration. To qualify for an unconditional registration, the registrant must submit a confirmatory Intraperitoneal Injection Study, OPPTS guideline # 885.3200.

E. Regulatory History

Prophyta Biologischer Pflanzenschutz GmbH, Germany (US Agent: WF Stoneman Co. LLC, Box 465, McFarland, WI 53558-0465) submitted an application for registration of MeloCon WG, a product containing the new active ingredient, *Paecilomyces lilacinus* strain 251. This application was announced in the Federal Register on November 14, 2003 (68 FR 64623-5) (FRL-7331-8). The company also filed a petition to establish a tolerance

exemption for *Paecilomyces lilacinus* strain 251 when used on crops; on November 7, 2003 (68 FR 63088-92) (FRL 7331-7), the Federal Register announced receipt of the petition. The microbe is approved for pesticide use in South Africa, New Caledonia, and Bulgaria, and is under consideration for approval by the European Union.

This document contains data supporting a conditional registration for MeloCon WG as a microbial nematicide product. A permanent exemption from the requirement of a tolerance for *Paecilomyces lilacinus* strain 251 was published in the Federal Register on April 13, 2005 (70 FR 19278-83) (FRL-7708-4)

On March 30, 2005, MeloCon WG (EPA Reg # 72444-2) was granted a conditional registration. The registration was announced in the Federal Register on June 3, 2005 (70 FR 32612-14) (FRL-7715-9).

III. SCIENCE ASSESSMENT

A. Physical and Chemical Properties Assessment

1. Microbe Characteristics:

The agency has approved the fungus *Paecilomyces lilacinus* strain 251 as a microbial pesticide active ingredient. MeloCon WG contains living conidia of *P. lilacinus* strain 251 as the active ingredient. This strain grows optimally at 21-27 degrees C, and does not grow or survive above 36 degrees C. Unlike many other *Paecilomyces lilacinus* strains, *P. lilacinus* strain 251 does not produce mycotoxins or paecilotoxins, as shown by laboratory analyses and lack of toxicity to mammals and other organisms.

2. Product Chemistry

Product chemistry data that support the registration of *P. lilacinus* strain 251 are summarized in Table 1.

Table 1. Physical and Chemical Properties for *P. lilacinus* strain 251

OPPTS GUIDELINE Number	STUDY	RESULT	MRID#
885.1100	Product Identity and Disclosure of Ingredients	Acceptable	463056-01
885.1200	Manufacturing Process	Acceptable	463056-01
885.1300	Formation of Unintentional Ingredients	Acceptable	463056-01
885.1400	Analysis of Samples	Acceptable	463056-01
885.1500	Certification of Limits	Acceptable	463056-01
830.6302, 830.6303, 830.6304, 830.7000, 885.7300	Product Chemistry	Acceptable	463056-01
Non- guideline study	Influence of Temperature on Germination of Spores	Spores survive 5 days at 36^0 C, and die at 37^0 C. Optimum growth occurs 21^0 to 27^0 C.	460292-01
Non-guideline study	Presence of Paecilotoxins	No evidence of known toxins was seen in chromatographic studies.	462832-03

B. Human Risk Assessment

There is a reasonable certainty that no harm will result from exposure to *P. lilacinus* strain 251. This includes all anticipated dietary exposures and all other exposures for which there is reliable information.

1. Human Toxicity Assessment

a. Acute Toxicity

All required mammalian toxicology/pathogenicity study results have been submitted or waived, and adequately satisfy data requirements to support registration. Details are provided below.

Table 2. Toxicity Data Requirements

OPPTS GUIDELINE NUMBER	STUDY	RESULT	MRID#
870.1100	Acute Oral Toxicity	LD_{50} oral toxicity of *P. lilacinus* strain 251 in rats is > 2000 mg/kg. **Toxicity Category III**, ACCEPTABLE;	462832-01
870.1200	Acute Dermal Toxicity	LD_{50} acute dermal toxicity of *P. lilacinus* strain 251 in rats is > 2000 mg/kg mg/kg. **Toxicity Category III** ACCEPTABLE	462832-02
885.3150	Acute Pulmonary Toxicity/ Pathogenicity (one intratracheal dose)	No signs of toxicity or pathogenicity were detected. ACCEPTABLE.	459418-04
885.3200	Acute Intraperitoneal Toxicity/Pathogenicity	SUPPLEMENTARY (Dose of test material not directly determined)	460042-01
870.2400	Primary Eye Irritation	No signs of irritation in rabbits. **Toxicity Category IV.** ACCEPTABLE.	460042-07
870.2500	Primary Dermal Irritation	No signs of irritation in rabbits. **Toxicity Category IV.** ACCEPTABLE	459418-06

OPPTS GUIDELINE NUMBER	STUDY	RESULT	MRID#
870.2600	Delayed Contact Hypersensitivity in Guinea Pigs	Not a dermal sensitizer. ACCEPTABLE.	459418-07
885.3400	Reporting Hypersensitivity Incidents	To be reported if any incidents occur	No incidents reported
880.3800	Immune Response	No evidence of adverse effects on immune response in various rodent studies.	WAIVED

Acute Oral Toxicity - Rat (870.1100; MRID 462832-01)

Methods: Five male and five female rats were dosed with the test material (2000 mg/kg body weight), administered as a 10% w/w suspension in water by gavage. The test animals were observed for clinical signs of toxicity post-dosing and once daily for 14 days. All animals were necropsied and organ weights were recorded.
Results: All animals survived the study. All animals gained weight during the study. No abnormal clinical signs and no gross abnormalities were noted. The oral LD_{50} for males, females, and combined was greater than 2000 mg/kg. This places Bioact *(Paecilomyces lilacinus*) batch No. 90228 in TOXICITY CATEGORY III. for oral toxicity.
Classification: ACCEPTABLE.

Acute Dermal Toxicity-Rat, (870.1200; MRID 462832-02)

Methods: The test material (2000 mg/kg body weight/animal) was applied to five male and five female rats on the clipped dorsal trunk in an area of 36 cm^2. The application site was covered with a 7.5 x 7.5 cm gauze patch held in place with hypoallergenic tape. The coverings were removed after 24 hours and the excess test material was removed with moistened gauze. The test animals were observed for clinical signs of toxicity frequently after treatment and once daily thereafter for 14 days. The rats were euthanized on day 15, but no necropsies were performed.

Results: All rats survived the study. No animals showed any clinical signs during the study. One female had very slight erythema on day 2 with clearance by day 3. All animals had normal body weight gain and there were no gross abnormalities at necropsy.
The dermal LD_{50} for males, females, and combined was greater than 2000 mg/kg. This places Bioact *(Paecilomyces lilacinus*), batch No. 90228 in TOXICITY CATEGORY III.. **Classification: ACCEPTABLE**.

Acute Intraperitoneal Injection Toxicity/Pathogenicity - Rat (885-3200; MRID 460042-01)

Methods: The analytical certificate of the test material states that the nominal content of the active ingredient was 2×10^9 cfu/g, and that the analytical content was 4.48×10^9 cfu/g. The testing laboratory did not confirm the analytic content before administering the test material to 5 male and 5 female rats by a single intraperitoneal dose of 2000mg/kg body weight.
Results:: No deaths were observed in the treated or control groups during the study.

- **Gross Necropsy:** Both control and test animals showed evidence of mycoplasmosis at necropsy. Findings included: hemorrhagic consolidation, pneumonic foci, hepatization of lungs, congested liver or liver with whitish foci, congested kidneys, cystic pancreas, enlarged spleen.
- **Infectivity Results:** The digestive tract of one test male and one test female had 270 and 290 cfu/organ, respectively, which was attributed to environmental contamination. No test organisms were detected in any of the test animals or in two control animals in the following organs: liver, kidney, spleen, lungs, brain, urinary bladder, lymphatic ganglia, or thymus.

Classification: **SUPPLEMENTARY (because of uncertainty of test dose)**

Acute Pulmonary Toxicity/Pathogenicity - Rat (885.3150; MRID 459418-04)

Methods: Test material was found to contain 6.5×10^9 viable spores/g. The test material was administered in a single intratracheal dose to 35 male and 35 female rats. The rats in Groups 2 through 7 received 0.05 mL (2.5×10^8 conidia) of Bioact®WG in 0.8% sodium chloride buffer solution.
Results: The presented data show no clinical signs in rats. *Paecilomyces lilacinus* was detected in lungs with clearance by day 15 after dosing, in lung lymph nodes with clearance by day 15 after dosing, and in tracheal lymph nodes with clearance by day 4 after dosing. The test organism was

also detected in cecal content probably due to swallowing of the test organism at dosing. *Paecilomyces lilacinus* was not detected in kidneys, liver, spleen, blood, brain, or lymph nodes (cervical and mesenteric). Necropsy studies showed no observable abnormalities due to the test organism. Therefore, based on the presented/submitted data, the test organisms were not toxic, infective, or pathogenic to rats.
Classification: ACCEPTABLE

Primary Eye Irritation - Rabbit (870.2400; MRID 460042-07)

Methods: For three male rabbits, the test material (100 mg/eye/animal) was applied in the conjunctival sac of one eye, and the other eye was instilled with 0.1 mL of distilled water as a control. The eyes were examined and scored 1, 24, 48 and 72 hours after test material instillation.
Results: All animals survived the study. No corneal opacity or iritis or any other signs of irritation were noted on any rabbit. TOXICITY CATEGORY IV.
Classification: ACCEPTABLE

Skin Sensitization - Guinea Pig (870.2600; MRID 459418-07)

Methods: Twenty guinea pigs were induced and challenged according to the method of Buehler, while 25 other animals served as positive and negative controls. The flank of all guinea pigs was clipped prior to each treatment. For the induction, approximately 0.5 g of test material moistened with water was applied epicutaneously and occluded for 6 hours. The procedure was repeated once each week for three consecutive weeks. Twelve days after the last induction, the test animals were challenged with 0.25 g of test material.
Results: No reaction was noted on any test animal after the first and the second inductions. A few animals showed confluent or non-confluent erythema 24 hours after the third induction. No positive reaction was noted on any test or naive control animals after challenge. The results of the DNCB positive control were appropriate. The product was not a dermal sensitizer. No deaths were observed in any group.
Classification: ACCEPTABLE.

Primary Dermal Irritation - Rabbit (870.2500; MRID 459418-06)

Methods: The fur on the dorsal trunk of three female rabbits was clipped on the day prior to treatment. For treatment, 0.5 g of test material was placed on a patch which was taped to the skin

for four hours. Dermal examination was recorded at 1, 24, 48, and 72 hours after removal of the patch.

Results: All rabbits survived the study. One rabbit had barely perceptible erythema one hour after patch removal with clearance by 24 hours. No dermal irritation was noted on any other rabbit. The primary irritation index was 0.33. *Paecilomyces lilacinus* strain 251 was essentially non-irritating and is in TOXICITY CATEGORY IV.

Classification: ACCEPTABLE.

Immune Response (880.3800) (WAIVED)

A waiver for an immune response study was granted, based on results of various rodent studies that showed no evidence of adverse effects to the immune system, as explained below (MRID # 462832-01; 459418-04).

Animal behavior and weight gain remained normal, and there was no excess morbidity or mortality in the studies. No organ abnormalities attributed to the test material were seen on necropsy. In a pulmonary pathogenicity study, the fungal titre in various organs decreased during the first 8 days after dosing, and clearance was complete by 14 days. This clearance provides evidence that the immune system was functioning, although a concomitant explanation is that the conidia became non-viable over time because they do not survive more than a few days at temperatures above 36°C. Taken together, these data indicate that *Paecilomyces lilacinus* strain 251 does not interfere with immune system function.

b. Subchronic Toxicity and Chronic Toxicity

Subchronic and chronic toxicity studies were not required because survival, replication, infectivity, toxicity, or persistence of the microbial agent was not observed in the treated animals in the acute studies.

c. Effects on the Endocrine and Immune Systems

Endocrine Systems. EPA is required under section 408(p) of the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally-occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there is no scientific basis for including, as part of the screening program, the androgen and thyroid hormone systems in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the program include

evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require wildlife evaluations.

When the appropriate screening and/or testing protocols being considered under the Agency's Endocrine Disruptor Screening Program have been developed, *P. lilacinus* strain 251 may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption. Based on the weight of the evidence of available data, no endocrine system-related effects have been identified for *P. lilacinus* strain 251.

Immune System. There is no evidence to suggest that *P. lilacinus* strain 251 has adverse effects on the immune systems of mammals or other non-target organisms tested. As expected from a non-toxic, non-pathogenic microorganism, the submitted studies in rodents using several routes of exposure indicate that the immune system remains intact. For example, all test animals remained healthy and maintained normal weight and behaviors during these studies. Although the pathogenicity data are consistent with clearance by an active immune system, an alternate explanation is that the test organisms died because they were exposed to temperatures beyond their survival range.

2. Dose Response Assessment

No toxicological responses have been identified. Therefore, a dose response assessment was not performed.

3. Dietary Exposure and Risk Characterization

Humans and animals are commonly exposed to *P. lilacinus* strain 251, an organism found in soil. No toxicological or pathological endpoints were identified for *P. lilacinus* strain 251, as demonstrated in Table 2, Toxicity Data Requirements of this document. These data are sufficient to support a tolerance exemption for this active ingredient.

4. Occupational, Residential, School, and Day Care Exposure and Risk Characterization

a. Occupational Exposure and Risk Characterization

Occupational exposure to *P. lilacinus* strain 251 is minimized by the use of personal protective equipment and a restricted reentry interval of 4 hours for treated areas.

b. Residential, School and Day Care Exposure and Risk Characterization

No indoor residential, school, or day care uses currently appear on the proposed label. Non-dietary human exposure to *P. lilacinus* strain 251 is not expected at these sites. In the absence of any toxicological/pathogenic endpoints, risk from the consumption of residues of *P. lilacinus* strain 251 from its pesticidal use on food is not expected for populations, including infants and children, in residential, school, and day care environments.

5. Drinking Water Exposure and Risk Characterization

No risks are expected from exposure to *P. lilacinus* strain 251 via drinking water because exposure will be minimum and the organism shows no harmful effects on animals that were exposed orally. The potential for transfer of *P. lilacinus* strain 251 to surface or ground water during run-off is considered minimal to non-existent, due to its slow movement in soil and its attachment to plant root nematodes. The organism is normally found in soil. Labels instruct users not to allow *P. lilacinus* strain 251 to enter bodies of water during use or disposal. Therefore, potential exposure to *P. lilacinus* strain 251 in surface and drinking water is negligible.

6. Acute and Chronic Dietary Risks for Sensitive Subpopulations, Particularly Infants and Children

FFDCA section 408 provides that EPA shall apply an additional tenfold margin of exposure (safety) for infants and children, in the case of threshold effects, to account for pre- and post-natal toxicity and the completeness of the database, unless EPA determines that a different margin of exposure will be safe for infants and children. Margins of exposure are often referred to as margins of safety or as uncertainty factors. EPA concludes that the toxicity and exposure data are sufficient to show that there is a reasonable certainty that no harm will result to infants and children from dietary exposure to *P. lilacinus* strain 251 residues. Because no threshold effects were detected, an additional safety factor is not required.

7. Aggregate Exposure and Risk from Multiple Routes Including Dermal, Oral, and Inhalation

a. Aggregate Exposure

In examining aggregate exposure, section 408 of the FFDCA directs EPA to consider available information concerning exposures from the pesticide residue in food and all other non-occupational